Clopidogrel (Plavix®) Criteria for Use in Veteran Patients

VHA Pharmacy Benefits Management Services and the Medical Advisory Panel

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient. Individual cases that are outside the recommendations should be adjudicated at the local facility according to the policy and procedures of its P&T Committee and Pharmacy Services

Exclusion Criteria

- ❑ Substantial risk of bleeding
- ❑ Known hypersensitivity to clopidogrel or any component of the product

Inclusion Criteria- one of the following indications is required

- ❑ Post percutaneous coronary intervention (PCI)/stent
- ❑ NSTEMI/Unstable angina acute coronary syndromes
- ❑ STEMI /acute coronary syndrome
- ❑ Coronary Artery Bypass Grafting (CABG)
- ❑ Cerebral ischemic events*
- ❑ Non-cardiac stenting
- ❑ Need for antiplatelet therapy but has a true aspirin allergy (ie; anaphylaxis or aspirin induced asthma) or extended release aspirin dipyridamole therapy induced headaches

Duration- please refer to Table 1(enter duration after indication)

- ❑ Post PCI/ bare metal stent _____
- ❑ Post PCI / DES stent_____
- ❑ NSTEMI/Unstable angina acute coronary syndromes _____
- ❑ STEMI /acute coronary syndrome _____
- ❑ Elective Coronary Artery Bypass Grafting (CABG) _____
- ❑ Brachytherapy _____
- ❑ Cerebral ischemic events _____
- ❑ Non-cardiac stenting _____
- ❑ Other_____

Monitoring

Patients should be followed for development of neutropenia and/or thrombotic thrombocytopenic purpura

Routine use of platelet function assays to monitor the antithrombotic effect of aspirin or clopidogrel is not recommended

* Clopidogrel therapy for a cerebral ischemia indication should be monotherapy only. Clopidogrel should not be combined with aspirin for this indication

Table 1:Clopidogrel dose and duration by indication

	clopidogrel dose	duration (strong evidence support)
aspirin allergy (Anaphylaxis, aspirin induced asthma)	75 mg daily	indefinite (for as long as antiplatelet therapy is required)
bare metal stent	300-600 mg load, then 75 mg daily	for at least one month, ideally up to 12 months
DES-uncomplicated	300-600 mg load, then 75 mg daily	12 months
DES complex anatomy*	300-600 mg load, then 75 mg daily	12 months, longer duration may be considered in absence of bleeding risk factors
DES-history of stent thrombosis	300-600 mg load, then 75 mg daily	give combination of aspirin clopidogrel indefinitely in absence of bleeding risk factors
ACS (no stent)	300-600 mg load, then 75 mg daily	12 months
NSTEMI/ACS (no stent)	75 mg daily	12 months
NSTE ACS then CABG	75 mg daily	9-12 months post procedure
STEMI/MI (no stent)	300 mg load for patients < 75 yrs and 75 mg for > 75 years if they receive fibrinolytics, then 75 mg daily for	at least 14 days and up to 12 months
cerebral ischemia	75 mg daily	indefinite- do not give aspirin and clopidogrel together
brachytherapy	75 mg daily	indefinite
intracranial stent	75 mg daily	3 months up to 1 year
extracranial stent#	75 mg daily	6 weeks
renal stent	75 mg daily	up to 12 months
peripheral (inguinal, popliteal) stent	75 mg daily	30 days

*Complex anatomy includes, but not limited to left main, multi vessel, bifurcation, kissing, overlapping stents, stent in coronary bypass graft artery

extracranial stent location is carotid artery

Background and Evidence for Clopidogrel (Plavix®) Criteria for Use

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Recommendations for use of clopidogrel post percutaneous coronary intervention (PCI)/stent

- Patients who receive coronary stents will require dual anti-platelet therapy with aspirin and clopidogrel in order to maintain patency of the artery.
- There is evidence that drug eluting stents (DES) may confer a rare but increased risk of late stent thrombosis in certain patient populations (including complex coronary anatomy such as: left main DES, DES of bifurcations, overlapping DES, prior history of late stent thrombosis, and DES of bypass graft), suggesting a longer duration of dual therapy may be needed. The exact duration of clopidogrel therapy in these situations has not been conclusively established, however when making this determination providers must weigh the benefit of prolonged or indefinite clopidogrel therapy against the risk for bleeding on a patient by patient basis
- Retrospective data supports that the most vulnerable period may be 0 to 90 days after discontinuation of clopidogrel. It has not been clearly defined if the use of a tapering schedule for discontinuation may alleviate this response.
- The optimal dose of aspirin remains controversial. There is no convincing evidence from randomized studies that have compared different doses of aspirin that higher doses are more effective in reducing the risk of serious vascular events. Higher doses of aspirin are associated with increased bleeding risk.
- Data emerging from pooled meta-analyses and registries suggest the need for uninterrupted dual antiplatelet therapy throughout the post-stenting treatment period. Any elective procedures which would require stopping or interrupting this therapy (dental work, colonoscopy, etc.) should be delayed until the minimum treatment duration based on stent type is completed.

Recommendations for use of clopidogrel in NSTEMI/Unstable angina acute coronary syndromes

- In patients with acute coronary syndrome and /or unstable angina in whom no revascularization procedure is planned, clopidogrel should be added to aspirin as soon as possible.

Recommendations for use of clopidogrel in STEMI acute coronary syndrome

- In patients with STEMI < 75 years of age receiving fibrinolytics, clopidogrel should be administered as a 300mg loading dose followed by 75mg once daily until hospital discharge (up to 8 days) or longer if undergoing angiography/coronary intervention as described in recommendations post PCI/Stent.
- In patients of any age with STEMI regardless of whether fibrinolytics are utilized clopidogrel should be administered at a dose of 75mg once daily until hospital discharge or up to 4 weeks or longer if undergoing angiography/coronary intervention as described in recommendations post PCI/Stent.
- In patients with STEMI who do not undergo PCI consideration may be given to continuing clopidogrel 75mg once daily for up to 1-year based on extrapolation from trials in NSTEMI/Unstable angina.

Recommendations for use of clopidogrel in stable coronary artery disease (CAD)

- There is insufficient evidence to recommend initiation in those patients with stable CAD and who do not meet criteria in this document.

Recommendations for use of clopidogrel in aspirin adverse events

- Clopidogrel should be used in patients who are aspirin allergic, i.e.; anaphylaxis, aspirin induced bronchospasm. (Level A)
- In patients with a history of gastrointestinal complications from aspirin (i.e.; bleeding, stomach upset), adding a proton pump inhibitor to aspirin therapy is preferred.

Recommendations for use of concurrent clopidogrel and proton pump inhibitor therapy

- Recent evidence suggests that genetic variables may be important in the metabolism/activation of clopidogrel. Early trials suggest a link between the cytochrome P450 system, especially the 2C19 isoenzyme and clopidogrel response.
- It is possible that patients with a decrease in 2C19 isoenzyme may not display an expected response to clopidogrel. Additionally, proton pump inhibitors (metabolized by the 2C19 isoenzyme) may alter a patient's response to clopidogrel.
- A nested case control study by Juurlink et, al demonstrated that combined therapy with clopidogrel and a PPI increased the risk of reinfarction, with an adjusted odds ratio 1.27 with a CI of 1.03-1.57.
- A retrospective cohort study of 8205 patients with ACS taking clopidogrel after discharge from 127 Veterans Affairs hospitals between October 1, 2003, and January 31, 2006. reported that patients taking clopidogrel after hospital discharge and prescribed PPI at any point during follow-up (n = 5244), periods of use of clopidogrel plus PPI (compared with periods of use of clopidogrel without PPI) were associated with a higher risk of death or rehospitalization for ACS (adjusted hazard ratio, 1.27; 95% CI, 1.10-1.46). following coronary stenting over 12 months:
- In a nationally representative, claims-based, observational study of 16,690 patients adherent and persistent to clopidogrel therapy was associated with a 51% greater risk of a CV event than clopidogrel alone.
- It does not appear that a single PPI is less likely than others to result in the potential interaction. Omperazole, esomeprazole, pantoprazole and lansoprazole were each associated with 39-61% greater risk of a CV event vs. clopidogrel alone.
- The FDA has issued a safety bulletin regarding this issue and is working with manufacturers to design a prospective trial to assess the interaction.
- Patients who are currently receiving therapy with a PPI and clopidogrel should be evaluated for the continued need for PPI therapy..

Recommendations on the use of dual antiplatelet therapy versus warfarin therapy in atrial fibrillation

- The ACTIVE-W trial was a comparison of warfarin with the combination of clopidogrel and aspirin in patients with atrial fibrillation. The results of ACTIVE-W demonstrated that use of a vitamin-K antagonist reduced the risk for stroke by 42% over clopidogrel and aspirin.
- The ACTIVE A trial enrolled patients who were considered unsuitable for warfarin therapy. These patients were then randomized to clopidogrel/aspirin vs. aspirin only. The reasons for not being an appropriate warfarin candidate were varied, and included poor control of the INR, multiple drug interactions, warfarin allergy and/or patient preference.
- The number needed to treat (NNT) from the ACTIVE-A trial is 111 (clopidogrel/aspirin vs. aspirin alone) this is in comparison to NNTs of 20-30 for trials evaluating stroke reduction in patients receiving warfarin vs. control from SPAF-1, SPINAF trials.
- Compared with aspirin alone, the combination of clopidogrel and aspirin in patients unsuitable for warfarin therapy reduces the risk of major vascular events but does so at an increased risk for major bleeding. The absolute difference for the reduction of major vascular events between the study treatment groups, is about 0.8% per year, and compares with the major bleeding rate, which is 0.7% per year.
- Those patients who are excluded from warfarin therapy due to excessive bleeding risk may have the same elevated bleeding risk with dual antiplatelet therapy (see ACTIVE W trial).
- Patients who should not be considered for dual antiplatelet therapy include low risk for thromboembolic disease, documented PUD within the previous 6 months, history of intracerebral hemorrhage, significant thrombocytopenia, or ongoing alcohol abuse.

- Frequently patients who are not felt to be candidates for warfarin therapy at one point in time may no longer have the same contraindications at a later date. These patients should be re-evaluated every 6 months to insure that ongoing use of dual antiplatelet therapy is appropriate.

Recommendations for the use of clopidogrel in Peripheral Vascular Disease (PVD)

- Clopidogrel is not recommended for PVD except in cases of aspirin allergy.

Recommendations for the use of clopidogrel in noncardiac stenting

- Patients who undergo carotid artery stenting may be initiated on clopidogrel 75 mg/day and continued for 4-6 weeks post stent.
- Patients who undergo intracranial stents may require longer durations of therapy and can be continued up to 1 year.
- Patients who undergo renal artery stenting may be initiated on clopidogrel 75 mg daily for up to 12 months post intervention.
- Patients who undergo other peripheral stents (inguinal, popliteal, etc) may be continued on clopidogrel 75 mg daily for 30 days post intervention.

Recommendations for the use of clopidogrel in recurrent cerebral ischemic events

- Patients with recurrence of cerebral ischemic events while on therapy with aspirin should be changed to an alternate antiplatelet agent.
- Both clopidogrel and extended release dipyridamole/aspirin have been proven superior to aspirin in separate trials.
- Extended release dipyridamole/aspirin was not able to demonstrate noninferiority to clopidogrel in a randomized, double blinded trial of stroke patients. The findings of the PRoFESS trial demonstrated a lack of evidence that either of the two treatments were superior to the other in prevention of recurrent stroke.
- Clopidogrel is an alternative for those patients who have had recurrent cerebrovascular events, who have a documented aspirin allergy, as mentioned above or are intolerant of extended release aspirin/ dipyridamole (recurrent headache).
- The combination of aspirin and clopidogrel is not advised for secondary stroke prophylaxis due to increased risk of adverse events demonstrated in the MATCH trial.

Alternate dosing regimens for clopidogrel

The question of increased dosing with clopidogrel in treatment refractory patients has been discussed. A clinical trial in Type 2 diabetes mellitus patients investigated the efficacy of BID dosing. They demonstrated that increasing the dose of clopidogrel to 150 mg per day is associated with enhanced antiplatelet effects as measured by platelet aggregation studies. These studies were not correlated to any clinical outcomes. In a previous AHA/ACC guidelines, the use of a clopidogrel 150mg per day is recommended if there is less than 50% inhibition of platelet aggregation or if the risk of subacute thrombosis would be catastrophic or lethal (unprotected left main, bifurcating left main or last patent coronary vessel, or patient who has survived an in-stent thrombosis despite compliance with clopidogrel 75mg daily). However, these same guidelines recommend against using platelet reactivity testing on a routine basis.

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